REMARKS

Claims 45-48 are amended to correct informalities in the claims and claims 49-57 are added herein. Support for new claims 49-57 is found in the original claims and in the specification. Hence no issues of new matter are presented herein. Upon entry of the amendment, claims 45-57 will be all the claims pending.

I. Claim Rejections Under 35 U.S.C. § 112

A. Failure to Describe In a Clear and Concise Manner

Claims 45-48 are rejected as allegedly failing to comply with the requirement of 35 U.S.C. § 112, first paragraph, that the specification "shall contain a written description of the invention...in such full, clear, concise and exact terms...to make and use same...." The Examiner states that the claimed subject matter as presented is not described in a clear and concise manner because of the numerous variables (e.g. W, Z, X, Y, etc...), their voluminous meanings, and the vast number of permutations and combinations involved and the numerous provisos.

The Examiner also states that the recitation for the treatment or prevention of virtually all central nervous system diseases, cardiovascular system diseases, kidney diseases and diseases associated with abnormal adrenal gland secretions, in conjunction with the complicated formula further adds to the lack of the conciseness of the claims.

Applicants respectfully traverse the rejection as improper based on the following. First, the Examiner's basis for rejection is not clear, i.e., whether the claims are rejected as unduly broad or whether the claims are rejected for failure to provide an adequate written description in

the specification. Basically, the Examiner asserts that the claims are not clear and concise because of the numerous variables and provisos, and diseases or conditions to be treated or prevented, which is considered to be a rejection as to the broadness of the scope of the claims as to (1) the claimed compounds of formula II and (2) the diseases or conditions to be treated or prevented.

With respect to the breadth of the claims, claims are to be given their broadest reasonable interpretation that is consistent with the disclosure in the specification. Thus, the proper inquiry under 35 U.S.C. § 112, 1st paragraph is whether the entire scope of the claims is enabled by the specification. This is an enablement issue and is discussed below.

If the Examiner is referring to the written description, Applicants point out that the description is presumed to be adequate, unless sufficient evidence or reasoning has been presented by the Examiner to rebut the presumption. Applicants submit that the Examiner has not met her burden of presenting evidence why a person of ordinary skill in the art would not recognize a description of the claimed invention in the specification with respect to the claimed compounds of formula II. Clearly, the specification provides adequate support for the claimed compounds (page 5, line 20 through page 7, line 9); the variables (page 10, line 21 through page 14 line 28; the provisos (page 16, line 3 through page 17, line 6); and the recited diseases and conditions (page 4, line 13 to page 5, line.2).

B. Lack of Enablement

Claims 45-48 are also rejected under 35 U.S.C. § 112 first paragraph, as containing non-enabled subject matter. It is the Examiner's position that the claims are not enabled for "the

prevention of disease of the central nervous system, cardiovascular diseases, glaucoma," and other diseases in claim 45 because it has not been shown in the specification that the testing protocol used is accepted in the art as being predictive of the alleged utility. Additionally, the Examiner states that the specification is not enabling for the prevention of all forms of the vast number of diseases, including diseases of the central nervous system and cardiovascular system, and glaucoma.

The Examiner also asserts that the art pertaining to the central nervous system, the cardiovascular system, and the eye remains highly unpredictable and that various forms of these disorders have different causative agents, involve different cellular mechanisms, and, consequently, differ in treatment protocol. Thus, it is the Examiner's position that based on the unpredictable nature of the invention and state of the prior art and the extreme breadth of the claims, one skilled in the art could not use the claimed invention without undue experimentation.

Applicants respectfully traverse the rejection and submit that in making a determination of enablement, the proper inquiry is whether one of ordinary skill in the art would be able to use the claimed invention without undue experimentation. The PTO bears the initial burden of setting forth a reasonable explanation as to why it believes that the scope of protection provided by the claim is not adequately enabled by the description of the invention provided in the specification of the application; this includes, providing sufficient reasons for doubting any assertions in the specification as to the scope of enablement. In view thereof Applicants submit that the Examiner has not met her burden of providing a reasonable basis to question the enablement provided for the invention with respect to the claimed compounds.

Further, a specification may be enabling without any working examples. See MPEP 2164.02. However, in this case, several examples of compounds of the claimed formula (II) are provided in the specification, thereby providing ample guidance for one skilled in the relevant art to make and/or use the claimed invention without undue experimentation. In this regard, there are 5 compounds exemplified in Table 2 of formula (II) on page 37 of the specification, although the activity at the oxazoline receptor is not limited to these exemplary compounds, which provide ample guidance for the skilled artisan.

With respect to the Examiner's grounds for rejection regarding the treatment and prevention of the claimed diseases and conditions, Applicants submit that most treatments for diseases such as hypertension also have a preventative action. However, in an effort to facilitate examination, Applicants have amended the claims by deleting the phrase "or prevention" in claims 45 and 47 as suggested by the Examiner.

Further, with respect to the treatment of the recited diseases and conditions, Applicants submit that the test for enablement is whether the disclosure in the specification is sufficient to enable one of ordinary skill in the art to practice the claimed invention without undue experimentation. The fact that experimentation is necessary is not conclusive of non-enablement but any necessary experimentation should not be undue. The following eight factors should be weighed and all of the evidence related to each of these factors should be considered as a whole in determining whether any experimentation would be undue:

1. Nature of invention;

2. State of prior art;

3. Level of ordinary skill in the art;

4. Level of predictability in the art;

5. Amount of direction and guidance provided by the invention;

6. Existence of working examples;

7. Breadth of claims; and

8. Quantity of experimentation needed to make or use the invention based on the content of the disclosure.

In this regard, Applicants submit that the activity of the claimed compounds is based upon the distribution of the oxazoline receptor in mammals and the observed relationships of the oxazoline receptor with other receptors having known activities as described in the present specification on pages 1-2. Further, the distribution of the receptors in mammalian tissue is provided on page 4, lines 3-11. Thus, the specification provides sufficient guidance for one of ordinary skill in the art to use the claimed compounds for the treatment of the recited diseases and conditions. In addition, Applicants provide the following information regarding the state of the art and the relationship between the various receptors and their therapeutic activities.

Imidazoline Receptor Binding Sites

Many imidazoline derivatives and structurally-related compounds bind not only to α-$_2$ adrenoceptors, but also to imidazoline receptors (I-receptors) which differ in structure, function and distribution from α_2-adrenoceptors. These I-receptor binding sites (I-RBS) have been classified into I_1- and I_2- receptor subtypes.

I_1-Imidazoline receptors: I_1-RBS commonly labeled using [^{3}H] p-aminoclonidine, are localized in the ventrolateral medulla of the human, rat and bovine brain. This site mediates, in part, the hypotensive effects of imidazolines such as clonidine, moxonidine and the oxazoline rilmenidine. Ligands at I_1-RBS also increase water and sodium secretion in the kidney and stimulate catecholamine release from bovine adrenal chromaffin cells.

I_2-Imidazoline Receptors: I_2-RBS have been commonly labeled in tissue membranes or sections using [^{3}H]idazoxan, however, new, high affinity radioligands such as [^{3}H]2-BFI are available. In rat brain the highest densities of I_2-RBS are found in the ependymal layer surrounding the ventricles, the arcuate and interpeduncular nuclei and specific nuclei of the brainstem. However, moderate levels of binding are also present throughout the cortex, basal ganglia, septum, hippocampus and amygdala. I_2-RBS are localized to the outer mitochondrial membrane and in the brain are associated predominantly with astrocytes through an association with the mitochondrial enzyme, monoamine oxidase B (MAO-B)[4].

A functional role for I_2-RBS has not been clearly established however I_2-site ligands inhibit Na+ uptake in kidney, inhibit NA release in rabbit aorta and pulmonary artery and inhibit monoamine oxidase in rat liver.

I_3-Imidazoline Receptors: The inventors' work has defined another imidazoline receptor subtype (here designated the I_3-RBS) that is preferentially labeled by the oxazoline, [^{3}H]rilmenidine and is distinct from both I_1- and I_2-RBS. A number of lines of evidence support the existence of this receptor.

- The kinetic and pharmacological characteristics of [^{3}H]rilmenidine binding in rat cerebral cortex and kidney membranes clearly distinguishes it from both I_1- and I_2RBS subtypes.

- The inventors have synthesized and tested a large number of new compounds and demonstrated that the affinity for the I3-receptor does not correlate with the affinity for any of the other receptors.
- Although the distribution of [^{3}H]rilmenidine binding in rat brain has some similarities to that of [^{3}H]idazoxan, notable differences are apparent in the hippocampus, a region involved in memory, where [^{3}H]rilmenidine binding is seen in the CAl pyramidal cell layer, and in the motor neurons of the brainstem and spinal cord, where [^{3}H]rilmenidine binding has a distinct punctuate character. Autoradiography with emulsion-coated sections has shown that the binding in the CAl region is associated with neuronal cell bodies. In aged rats and in rats subjected to a model of stroke, this region shows increased I3 receptor density suggesting that this receptor is involved in processes of neuronal degeneration and decay.
- In rat kidney, high density [^{3}H]rilmenidine binding is localized in the cortex and outer stripe of the outer medulla. I_1- and I_2-RBS ligands, [^{3}H]p-aminoclonidine and [^{3}H]idazoxan, label only a_2-adrenoceptor sites in the inner medulla and inner stripe and do not detect any non-adrenergic sites.
- In rat brain cortical membranes [^{3}H]rilmenidine binding is enriched in the plasma membrane fraction, in contrast to [^{3}H]2BFI binding and monoamine oxidase (MAO-B) which are enriched in the mitochondrial fraction. This also differentiates the I3 receptor and indicates it is expressed on the cell surface.
- I_3-RBS have been confirmed in human brain and human adrenal cortex and preliminary studies in human brain have shown that in areas damaged by Parkinson's disease, the ratio of 13-binding per neuronal cell is increased, but unchanged in unaffected areas such as frontal

cortex. This fits with our observations in rat brain that the binding is increased following stroke or in aged animals.

In view of the above, Applicants submit that in view of the eight factors set forth above, particularly in view of the nature of the invention, state of the prior art, level of skill in the art, and the guidance and working examples provided in the specification, one of ordinary skill in the art is sufficiently enabled to practice the claimed invention. Accordingly, Applicants respectfully request withdrawal of the rejection.

II. Claim Rejections Under 35 U.S.C. § 112, 2nd Paragraph

Claim 12 is rejected under 35 U.S.C. § 112, 2nd paragraph as allegedly indefinite because of the recitation of the phrase "such as" in claim 46.

Applicants have amended claim 46 to delete the phrase "such as" and added new claims 49 and 50, each dependent on claim 46, directed to degenerative conditions and neurodegenerative diseases, respectively, thereby obviating the rejection.

Accordingly, Applicants respectfully request withdrawal of the rejection.

III. Abstract

The Examiner objected to the Abstract as improper. Applicants have amended the Abstract in accordance with the Abstract set forth in corresponding International Publication No. WO 99/224411.

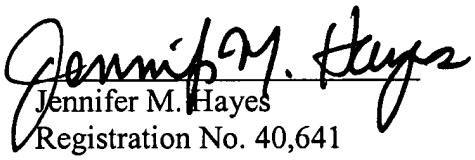
Accordingly, Applicants respectfully request withdrawal of the objection.

IV. Conclusion

In view of the above, reconsideration and allowance of this application are now believed to be in order, and such actions are hereby solicited. If any points remain in issue which the Examiner feels may be best resolved through a personal or telephone interview, the Examiner is kindly requested to contact the undersigned at the telephone number listed below.

The USPTO is directed and authorized to charge all required fees, except for the Issue Fee and the Publication Fee, to Deposit Account No. 19-4880. Please also credit any overpayments to said Deposit Account.

Respectfully submitted,



Jennifer M. Hayes
Registration No. 40,641

SUGHRUE MION, PLLC
2100 Pennsylvania Avenue, N.W.
Washington, D.C. 20037-3213
Telephone: (202) 293-7060
Facsimile: (202) 293-7860
Date: October 1, 2002

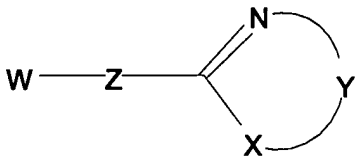
APPENDIX

VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE CLAIMS:

The claims are amended as follows:

45. (Amended) A method for the treatment ~~or prevention of~~ diseases of the central nervous system (excluding those involving CNS depressant action), the cardiovascular system (excluding hypertension), ~~or of~~ the kidney, or diseases associated with abnormal adrenal gland secretions, or ~~in~~ for the treatment of hyperglycaemia or peptic ulcer, which comprises administering an effective amount of a compound of formula II:



II

wherein W is optionally substituted aryl; optionally substituted C_5-C_7 cycloalkyl; -CHR^1R^2 where R^1 and R^2 are independently selected from hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_3-C_7 cycloalkyl and optionally substituted aryl; OR' where R' is optionally substituted aryl; optionally substituted C_3-C_7 cycloalkyl; or optionally substituted C_1-C_6 alkyl; provided that R^1 and R^2 are not both hydrogen;

Z is imino, C_1-C_2 alkylene, -CH_2NH- or -CH_2CH_2NH-;

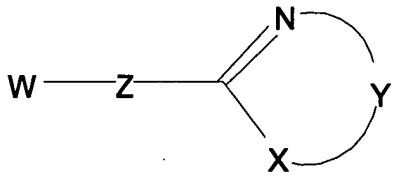
X is O or S; and

Y is optionally substituted C_2-C_3 alkylene; provided that W is not OR' when Z is imino or - CH_2NH-;

or a pharmaceutically acceptable salt or ester thereof.

46. (Amended) ~~A~~ The method according to claim 45 wherein the disease is a disease of the central nervous system ~~is~~ selected from the group consisting of dementia, mood disturbances, degenerative conditions ~~such as stroke, or aging, ischaemia, CNS trauma,~~ and neurodegenerative diseases ~~such as Alzheimer's disease and Parkinson's disease~~.

47. (Amended) A method ~~of~~ for the treatment ~~or prevention~~ of glaucoma comprising administering an effective amount of a compound of formula II



II

wherein W is optionally substituted aryl; optionally substituted C_5-C_7 cycloalkyl; -CHR^1R^2 where R^1 and R^2 are independently selected from hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_3-C_7 cycloalkyl and optionally substituted aryl; OR' where R' is optionally substituted aryl; optionally substituted C_3-C_7 cycloalkyl; or optionally substituted C_1- C_6 alkyl; provided that R^1 and R^2 are not both hydrogen;

Z is imino, C_1-C_2 alkylene, -CH_2NH- or -CH_2CH_2NH-;

X is O or S; and

Y is optionally substituted C_2-C_3 alkylene; provided that W is not OR' when Z is imino or -CH_2NH-; and

with the further provisos that

a) when Y is CH_2CH_2, X is O and Z is imino then

(i) if W is CHR^1R^2 and R^1 is H then R^2 is not selected from phenyl; phenyl substituted with methoxy, Br, Cl, F or trifluoromethyl; 3-nitrophenyl; 3- or 4-methylphenyl; 2- or 4-bromomethyl phenyl; 2- or 4-chloromethylphenyl; or 2,3- or 2,6-dimethylphenyl; and

(ii) if W is CHR^1R^2 and R^1 is CH_3 or cyclopropyl then R^2 is not phenyl or phenyl substituted with alkyl, halomethyl, fluoro or trifluoromethyl; and

b) when Y is $(CH_2)_{2-4}$, X is O or S, Z is imino and W is CHR^1R^2, then

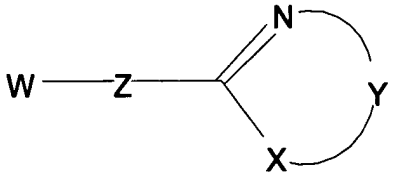
(i) if R^1 is CF_3, CF_2CF_3 or $CF_2CF_2CF_3$ then R^2 is not alkyl, optionally substituted cycloalkyl or optionally substituted aryl, and

(ii) if R^1 is optionally substituted cyclopropyl, R^2 is not H, alkyl or optionally substituted cyclopropyl;

or a pharmaceutically acceptable ester or salt thereof, to a subject in need thereof.

48. (Amended) A method for the treatment of diseases of the central nervous system, cardiovascular system, or the kidney, or <u>for the treatment of</u> diseases associated with abnormal

adrenal gland secretions, or in the treatment ~~or prevention~~ of hyperglycaemia, glaucoma, peptic ulcer or to produce analgesia which comprises administering an effective amount of a compound of formula II



II

wherein W is optionally substituted aryl; optionally substituted C_5-C_7 cycloalkyl; -CHR^1R^2 where R^1 and R^2 are independently selected from hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_3-C_7 cycloalkyl and optionally substituted aryl; OR' where R' is optionally substituted aryl; optionally substituted C_3-C_7 cycloalkyl; or optionally substituted C_1-C_6 alkyl; provided that R^1 and R^2 are not both hydrogen;

Z is imino, C_1-C_2 alkylene, -CH_2NH- or -CH_2CH_2NH-;

X is O or S; and

Y is optionally substituted C_2-C_3 alkylene; provided that W is not OR' when Z is imino or -CH_2NH-; and

with the further provisos that

a) when Y is CH_2CH_2, X is O and Z is imino then

(iv) W is not unsubstituted or 2-mono-, 2,2-di, 2,5-di, 2,6-di or 2,4,6-tri C_{1-3} alkyl substituted cyclohexyl or 2-mono- or 2,5,-di C_{1-3} alkyl substituted cyclopentyl or 2-C_{1-3} alkyl substituted cycloheptyl; and

(v) if W is CHR^1R^2 and R^1 is H then R^2 is not selected from phenyl; phenyl substituted with methoxy, Br. Cl, F or trifluoromethyl; 3-nitrophenyl; 3- or 4-methylphenyl; 2- or 4-bromomethylphenyl; 2- or 4-chloromethylphenyl; or 2,3- or 2,6 dimethylphenyl; and

(vi) if W is CHR^1R^2 and R^1 is CH_3 or cyclopropyl then R^1 is not phenyl or phenyl substituted with alkyl, halomethyl, fluoro or trifluoromethyl; and

b) when Y is $(CH_2)_{2-4}$, X is O or S, Z is imino and W is CHR^1R^2, then

(i) if R^1 is CF_3, CF_2CF_3 or $CF_2CF_2CF_3$ then R^2 is not alkyl, optionally substituted cycloalkyl or optionally substituted aryl, and

(ii) if R^1 is optionally substituted cyclopropyl, R^2 is not H, alkyl or optionally substituted cyclopropyl;

or a pharmaceutically acceptable ester or salt thereof, to a subject in need thereof.

Please add new claims 49-57.